IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PERNIX IRELAND PAIN DAC and PERNIX THERAPEUTICS, LLC,	)	
Plaintiffs,	)	C.A. No. 16-139-WCB
v.	)	
ALVOGEN MALTA OPERATIONS LTD.,	)	[redacted]
Defendant.	)	PUBLIC VERSION FILED: March 29, 2018

OPENING BRIEF IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT

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I. NATURE AND STAGE OF PROCEEDINGS

Plaintiffs ("Pernix") sued Alvogen for infringement of patents that cover Pernix's Zohydro® ER.[1] Alvogen seeks to sell infringing generic copies of Zohydro® ER before the patents-in-suit expire.

II. SUMMARY OF THE ARGUMENT

There are no genuinely disputed material facts regarding infringement. Pernix should thus be granted summary judgment of infringement, which will narrow the issues for trial to the validity of the asserted claims.

1. The patents-in-suit claim methods of treating pain in patients with mild or moderate hepatic impairment by administering an extended-release hydrocodone product such that there is no need to reduce the starting dose compared to that given to a patient without hepatic impairment. Alvogen's proposed product label for its generic copies of Zohydro® ER, [redacted], induces physicians and patients to practice the patented methods. Because Alvogen cannot genuinely dispute that it intends that physicians and patients follow its proposed product label, Alvogen will induce infringement.

2. Alvogen offers two non-infringement positions. First, Alvogen argues that some (but not all) of the asserted claims must be jointly practiced by a physician and patient, and that the physician does not direct or control administration of the drug by the patient. That theory fails because each asserted claim can be directly infringed by a single actor, the patient. And even if the claims are interpreted to require two actors, *i.e.*, a physician and a patient, there

[1] Pernix dropped patents and claims to narrow the issues in the case, and currently asserts claims 1-4, 11-12, 17 and 19 of U.S. Patent No. 9,265,760 ("the '760 patent"), and claim 1 of U.S. Patent No. 9,339,499 ("the '499 patent") (collectively, the "asserted claims" of the "patents-in-suit."). The patents-in-suit share a common specification.

is no genuine dispute that those actors will jointly practice the asserted claims when a patient administers Alvogen's proposed ANDA product under the direction and control of his or her physician in accordance with Alvogen's proposed product label.

3. Second, Alvogen argues that the instructions in its proposed product label cannot show intent to induce infringement because those instructions were required or suggested by the FDA. The Federal Circuit rejected that argument in *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060-61 (Fed. Cir. 2010) (FDA requirements do not absolve an ANDA owner of specific intent to induce infringement). Alvogen's "decision to continue seeking FDA approval of those instructions" is "sufficient evidence of specific intent to induce infringement." *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1368 (Fed. Cir. 2017). There is no genuine dispute that Alvogen has the specific intent to induce—and will induce—infringement of the asserted claims.

III. STATEMENT OF FACTS

A. The Patents-in-Suit and Zohydro® ER

Pain is the most common reason for doctor visits in the United States. Ex. A ('760 patent) at col. 1:33-37.[2] It can be acute, lasting until the underlying condition is healed or removed, or chronic, persisting for years. *Id.* Physicians prescribe Pernix's Zohydro® ER, an extended release ("ER") formulation containing hydrocodone (an opioid), to manage pain severe enough to require daily, around-the-clock, long-term treatment for which alternative treatment options are inadequate. *Id.* at 1:48. Hepatic impairment (*i.e.*, reduced liver function) complicates treatment of pain because the liver metabolizes (breaks down) most opioids. So the same dose of an opioid generally leads to higher blood levels of drug (C_{max} and AUC) in

[2] Unless otherwise indicated, "Ex." refers to an exhibit attached to the Declaration of Zachary Garrett, Esq.

hepatically impaired patients compared to patients without hepatic impairment,[3] meaning that hepatically impaired patients receive too much drug (*i.e.*, an overdose), which can cause sedation, respiratory depression, or death. *Id.* at 2:44-47. Thus, physicians ***decrease*** the starting dose of opioids in patients with hepatic impairment to counter the effect of reduced liver function. *Id.* at 2:52-56. Doing so, however, complicates treatment. Unable to rely on the starting dose known to provide safe and effective pain relief in the normal patient population, physicians instead must monitor each hepatically impaired patient individually while adjusting dosages to try to safely achieve efficacy on a case-by-case basis.

ER formulations like Zohydro® ER release their active ingredient over a longer time compared to immediate release ("IR") formulations. The patents-in-suit describe five prior art commercial ER opioids that required dosage adjustments when administered to hepatically impaired patients. *Id.* at 3:10-4:29. Additionally, the patents-in-suit discuss the 2013 Bond Abstract with data on another hydrocodone ER formulation. That product, which was later approved by the FDA as Teva's Vantrela™ ER, had a clinically significant difference in AUC in patients with moderate hepatic impairment. In particular, "the delivery of ***[ER] hydrocodone***…led to ***systemic exposure to hydrocodone*** [AUC] ***that was ~70% higher in subjects with moderate hepatic impairment vs normal hepatic function***." *Id.* at 2:56-65. Such increases in AUC or C_{max} "can lead to many problems, including need for adjusting dose, complications for physicians in prescribing, need for liver function tests, lack of availability of correct doses, lack of availability of certain medications to those with hepatic impairment, and overdosing." *Id.* at 4:30-36. The increase in AUC seen with the Vantrela™ ER hydrocodone

[3] C_{max} and AUC are pharmacokinetic ("PK") parameters that measure how well and quickly the body breaks down a drug. C_{max} refers to the maximum concentration of drug in the patient's blood, and AUC (Area Under the Curve) is a measure of total exposure to the drug over time. *Id.* at 11:12-23.

product required a label instruction stating that patients with mild or moderate hepatic impairment should "[i]nitiate therapy with ***one half of the recommended initial dose*** and titrate carefully." Ex. D at 1 (emphasis added).

The inventors of the patents-in-suit unexpectedly found that physicians could prescribe the ***same*** starting dose of certain hydrocodone ER compositions in patients with and without hepatic impairment, thus providing a safer and simpler way of treating those patients. *Id.* at 4:40-65. Administration of those ER compositions minimizes the increase in AUC and C_{max} that one normally expects in hepatically impaired patients, rendering that increase "not clinically significant." *Id.* at 5:37-41, 23:27-38.

The asserted claims recite methods of treating pain in a patient with mild or moderate hepatic impairment by administering an ER hydrocodone oral dosage unit. The claims require particular PK profiles for patients with mild and moderate hepatic impairment, and/or require no adjustment in the starting dose for patients with mild and moderate hepatic impairment relative to patients without hepatic impairment. *See* Claim Charts, Sections IV(B)(2) and IV(C)(3).

B. Alvogen's ANDA Product

Alvogen filed an Abbreviated New Drug Application ("ANDA") with the FDA seeking to market generic copies of Zohydro® ER ("Alvogen's ANDA Product"). D.I. 48 (Alvogen's Answer) at ¶ 14. As part of its ANDA filing, Alvogen submitted a proposed product label that will be included with Alvogen's ANDA Product ("Alvogen's Label"). *See* Ex. C. [redacted]

[redacted]

C. Claim Construction

Each of the asserted claims include the term "administering," which Judge Sleet construed to mean "delivering into the body." D.I. 69 (Claim Construction Opinion) at 1. Asserted claims 1-4 and 11 of the '760 patent also include the limitation "wherein the starting dose is not adjusted relative to a patient without hepatic impairment." Judge Sleet construed that limitation to mean "wherein the dose prescribed to a patient with mild or moderate hepatic impairment when initiating treatment is not reduced due to that hepatic impairment relative to the dose prescribed to a patient without hepatic impairment when initiating treatment." *Id.* at 2.

IV. ARGUMENT

A. Legal Standard

Summary judgment under Rule 56 of the Federal Rules of Civil Procedure should be granted "if the movant shows that there is no genuine dispute as to any material fact and the

movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a).

Once the moving party shows that no genuine dispute of material fact exists, the burden shifts to the non-moving party to offer admissible evidence that establishes a genuine issue of material fact, *Celotex Corp. v. Catrett*, 477 U.S. 317, 324 (1986), not just some "metaphysical doubt as to the material facts." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986). The substantive law identifies which facts are "material." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986).

A party who "actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). Induced infringement "must be predicated on direct infringement," *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1364 (Fed. Cir. 2017) (quotations omitted), and "requires that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056 (Fed. Cir. 2010) (quotations omitted).

In the Hatch-Waxman context, courts have repeatedly held that an ANDA product label that encourages, recommends, or promotes direct infringement is sufficient to demonstrate specific intent to induce infringement by the ANDA owner. *See, e.g.*, *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 644 (Fed. Cir. 2017) ("When proof of intent to encourage depends on the label accompanying the marketing of a drug, '[t]he label must encourage, recommend, or promote infringement.'"); *Eli Lilly*, 845 F.3d at 1368-69; *Braintree Labs., Inc. v. Breckenridge Pharm., Inc.*, 688 F. App'x 905, 908-910 (Fed. Cir. 2017); *AstraZeneca*, 633 F.3d at 1057-1061; *Hoffman-La Roche Inc. v. Apotex Inc.*, 2010 U.S. Dist. LEXIS 92264, at *14-22 (D.N.J. Sept. 2, 2010) (summary judgment of induced infringement based on instructions in ANDA label); *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 676 F. Supp. 2d 352, 376-79 (D.N.J. 2009) (same), *aff'd in*

relevant part 435 F. App'x 917, 926-27 (Fed. Cir. 2011); *Wyeth v. Sandoz, Inc.*, 703 F. Supp. 2d 508, 518-21 (E.D.N.C. 2010) (same).

B. Alvogen Induces Infringement of '760 Patent Claims 12, 17 and 19 and '499 Patent Claim 1

Alvogen will induce patients to directly infringe '760 patent claims 12, 17 and 19 and '499 patent claim 1 because Alvogen's Label encourages, recommends, and promotes that infringement.

1. Patients directly infringe '760 patent claims 12, 17 and 19 and '499 patent claim 1

As an initial matter, '760 patent claims 12, 17 and 19 and '499 patent claim 1 include only one step. For example, claim 12 recites the step "***administering*** to the patient having mild or moderate hepatic impairment an oral dosage unit having hydrocodone bitartrate as the only active ingredient…." There is no dispute that these claims are performed by a single actor, the patient. Specifically, the claims require a patient to administer (*i.e.*, deliver into his or her body) a drug product that meets the claim limitations. *See* Ex. A ('760 patent) at claims 12, 17, 19; Ex. B ('499 patent) at claim 1. [redacted]

There is also no dispute that some patients who will administer Alvogen's ANDA Product will have mild or moderate hepatic impairment. Alvogen's expert, Dr. Candiotti, only asserts that "a large majority" of patients receiving Alvogen's ANDA Product will not have these conditions. Ex. E (Candiotti Rebuttal Report) at ¶ 70. In other words, Alvogen's expert conceded that some patients receiving Alvogen's ANDA Product will have mild or moderate hepatic impairment. In fact, Alvogen's Label [redacted]

[redacted] Alvogen's intent to induce these patients to infringe the claims, as explained below, is sufficient to establish that Alvogen has the requisite intent for inducement under 35 U.S.C. § 271(b). *Eli Lilly*, 845 F.3d at 1369 (finding requisite intent where ***some*** physicians would infringe claims); *AstraZeneca*, 633 F.3d at 1060 (same); *Sanofi v. Glenmark Pharms., Inc.*, 204 F. Supp. 3d 665, 680 (D. Del. 2016) (same).

2. Alvogen intends to induce infringement of ’760 patent claims 12, 17 and 19 and ’499 patent claim 1

[redacted]

As demonstrated in the claim charts below, patients with mild or moderate hepatic impairment will directly infringe ’760 patent claims 12, 17 and 19 and ’499 patent claim 1 upon administration of Alvogen's ANDA Product, and Alvogen intends this result:

’760 Patent, Claim 12	Alvogen's ANDA Product
"A method of treating pain"	[redacted]
"in a patient having mild or moderate hepatic impairment, the method comprising: administering to the patient having mild or moderate hepatic impairment"	

	[redacted]
"an oral dosage unit having hydrocodone bitartrate as the only active ingredient,"	
"wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate,"	
"wherein the dosage unit provides a release profile of hydrocodone that: (1) does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%;"	
"(2) does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 30%;"	
"(3) does not increase average hydrocodone C_{max} in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 9%;"	
"and (4) does not increase average hydrocodone C_{max} in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%."	
'760 Patent, Claim 17	
"The method of claim 12,"	
"wherein the dosage unit provides a release profile of hydrocodone such that: (1) the average hydrocodone $AUC_{0\text{-}inf}$ per 20 mg of	

hydrocodone bitartrate dosed to subjects not suffering from renal or hepatic impairment is in the range of about 300 ng*h/mL to about 500 ng*h/mL;"	[redacted]
"(2) the average hydrocodone $AUC_{0\text{-}inf}$ per 20 mg of hydrocodone bitartrate dosed to subjects suffering from mild hepatic impairment is in the range of about 300 ng*h/mL to about 570 ng*h/mL; and"	
"(3) the average hydrocodone $AUC_{0\text{-}inf}$ per 20 mg of hydrocodone bitartrate dosed to subjects suffering from moderate hepatic impairment is in the range of about 300 ng*h/mL to about 700 ng*h/mL."	
'760 Patent, Claim 19	
"The method of claim 17,"	
"wherein the dosage unit provides a release profile of hydrocodone such that the average hydrocodone $AUC_{0\text{-}inf}$ per 20 mg of hydrocodone bitartrate dosed to subjects suffering from moderate hepatic impairment is in the range of about 352 ng*h/mL to about 666 ng*h/mL."	
'499 Patent, Claim 1	
"A method of treating pain"	
"in a patient having mild or moderate hepatic impairment, the method comprising: administering to the patient having mild or moderate hepatic impairment"	
"an oral dosage unit having hydrocodone bitartrate as the only active ingredient,"	

"wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate,"	[redacted]
"wherein the dosage unit provides a release profile of hydrocodone that: does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%;"	
"and does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 30%."	

As the claim charts above make clear, there is no genuine dispute that patients with mild or moderate hepatic impairment will directly infringe '760 patent claims 12, 17 and 19 and '499 patent claim 1 upon administration of Alvogen's ANDA Product, and Alvogen intends this result. Alvogen is liable for induced infringement of these claims.

C. Alvogen Induces Infringement of '760 Patent Claims 1-4 and 11

1. Patients directly infringe '760 patent claims 1-4 and 11

'760 patent claims 1-4 and 11 recite the step of "administering to the patient having mild or moderate hepatic impairment a starting dose of an oral dosage unit having hydrocodone bitartrate as the only active ingredient…." As with the claims discussed above, this step is performed by a patient self-administering a drug product that meets the claim limitations.

Alvogen, however, argues that there is a second step in the body of claims 1-4 and 11 (namely "wherein the starting dose is not adjusted relative to a patient without hepatic impairment"). From this, Alvogen alleges that claims 1-4 and 11 can only be jointly infringed

because they allegedly require a physician to select a starting dose and a patient to self-administer the drug product. Ex. G (Interrogatory Responses) at 9.[4]

This issue was recently addressed in this District with regard to the following claim:

> A method of treating overweight or obesity, comprising administering a weight loss effective amount of a first and second compound to an individual who has been diagnosed as suffering from overweight or obesity in order to treat said overweight or obesity….

Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc., 2017 U.S. Dist. LEXIS 169570, at *4 (D. Del. Oct. 13, 2017).[5] There, the ANDA filer argued that the claim required both the act of a physician diagnosing a patient and the act of a patient administering the drug product. The Court disagreed:

> I agree that a diagnosis is required, but I disagree that this comprises a step in the method claim. A plain reading of this claim limitation indicates that the individual will already be diagnosed prior to the method being performed. The method itself requires only the single step of administering the drug.

2017 U.S. Dist. LEXIS 169570, at *42.

Thus, in *Orexigen*, the Court found that the claim limitation of diagnosing the patient as "suffering from overweight or obesity" was done "prior to the method being performed." The same reasoning is applicable here. Judge Sleet (and Pernix) recognized that "wherein the starting dose is not adjusted relative to a patient without hepatic impairment" is a claim limitation and integral to the claims because it has "an effect ***on how the administering step is performed***" and "patients with hepatic impairment ingest a different dose than they normally

[4] Alvogen's "joint infringement" defense is only applicable to claims 1-4 and 11, and not claims 12, 17 and 19 of the '760 patent, or claim 1 of the '499 patent. Ex. G (Interrogatory Responses) at 10-11.

[5] *Orexigen* was decided in October 2017, after claim construction briefing was complete and after Judge Sleet issued his claim construction decision in this case.

would, given the prior art." D.I. 69 (Claim Construction Opinion) at 3 (emphasis added); *see also* D.I. 65 (Pernix Answering Claim Construction Brief) at 2 (the step of the physician selecting the dose "is integral to the claimed method…."). As in *Orexigen*, that dose is determined "prior to the method being performed."

Alvogen's position fails to consider that fundamentally these claims are no different from other method of treatment claims, *e.g.*, a method of treating a patient suffering from a disorder, comprising administering a drug to a patient suffering from that disorder, wherein the dose of the drug is within a particular range. Here, the claims in essence recite: a method of treating pain in a patient with mild or moderate hepatic impairment, comprising administering hydrocodone to such a patient wherein the starting dose of hydrocodone is not adjusted relative to a patient who does not suffer from hepatic impairment. In either case, identifying the starting dose, whether within a range or "not adjusted," is a predicate to performing the claimed administering step, which is performed by the patient. While a physician must determine and prescribe the dose of the drug product before a patient can administer it, as in *Orexigen*, that action will already have been completed prior to performance of the claimed method (*i.e.*, prior to the patient "administering" the drug product). Joint infringement, therefore, is not required for '760 patent claims 1-4 and 11.

2. Patients and physicians act as a single entity <u>that directly infringes '760 patent claims 1-4 and 11</u>

As explained above, the methods in '760 patent claims 1-4 and 11 are performed by a single actor, the patient. However, even under a reading where both a patient and a physician are required to perform the claimed methods, summary judgment remains appropriate because there is no genuine dispute that patients and physicians will jointly practice the claims.

When no single actor performs all steps of a method claim, direct infringement occurs if "the acts of one are attributable to the other such that a single entity is responsible for the infringement." *Eli Lilly*, 845 F.3d at 1364 (quotations omitted). A physician and patient jointly infringe a claimed method if the physician "direct[s] or controls" the patient. *Id*. This direction and control occurs when a physician (1) "conditions participation in an activity or receipt of a benefit" upon the patient's performance of one or more steps of a patented method, and (2) "establishes the manner or timing of that performance." *Id.* at 1365 (quotations omitted). Based on undisputed evidence, including testimony from Alvogen's expert Dr. Candiotti, both conditions are met here.

First, physicians prescribing Alvogen's ANDA Product will condition continued treatment for chronic pain (*i.e.*, receipt of a benefit) on the patient administering Alvogen's ANDA Product as prescribed (*i.e.*, performance of a claim step). *See Eli Lilly*, 845 F.3d at 1365-67 (physician conditioned receipt of treatment on the patient performing the claimed step of taking a precursor medication). Dr. Candiotti admitted that because Alvogen's ANDA Product is a controlled substance, physicians will enter into written or oral agreements with their patients prior to prescribing Alvogen's ANDA Product. Ex. F (Candiotti Dep.) at 139:15-142:10, 78:22-84:5; Ex. E (Candiotti Rebuttal Report) at ¶ 30. Such agreements are mandated by law in some States. Ex. F (Candiotti Dep.) at 81:14-84:5; Ex. I (Florida Statute § 456.44) at 2. These agreements expressly condition continued treatment on the patient administering Alvogen's ANDA Product as prescribed, for example:

> Continuation of the medication is based on evidence of …compliance with instructions on[] usage of the medication. I have also been informed by my physician that continuation…of the medication will be determined by…adherence to usage restrictions.
>
> …I UNDERSTAND AND AGREE THAT FAILURE TO ADHERE TO THESE POLICIES WILL BE CONSIDERED

NONCOMPLIANCE AND MAY RESULT IN CESSATION OF OPIOID PRESCRIBING BY MY PHYSICIAN[.]

Ex. H (Consent form) (capitalization in original); Ex. F (Candiotti Dep.) at 139:15-142:10, 78:22-84:5; Ex. I (Florida Statute § 456.44) at 2 (agreement must state that non-compliance may result in discontinuation of medication). Alvogen only argues that, despite these agreements, a physician "has no way of knowing whether the patient is going to take the [medication]." Ex. G (Interrogatory Responses) at 10. But this is irrelevant because "conditioning" does not require a physician to "verify compliance" or "double-check another's performance."[6] *Eli Lilly*, 845 F.3d at 1366.

Second, physicians will establish the manner and timing in which patients will administer Alvogen's ANDA Product. Alvogen's expert, Dr. Candiotti, admitted that a physician will "give instruction and guidance as to when to take the medication and how to take it." Ex. F (Candiotti Dep.) at 158:14-18, 155:19-156:8, 158:25-159:20. [redacted]

Therefore, as explained below, physicians and patients will jointly practice '760 patent claims 1-4 and 11 when a patient with mild or moderate hepatic impairment administers

[6] Although not required to show "conditioning," physicians will take steps to ensure that patients administer Alvogen's ANDA Product. For example, during a patient's follow-up visit after receiving a prescription for an opioid drug, physicians conduct a urinalysis to make sure that the patient has been taking the medication as prescribed. Dr. Candiotti acknowledged this practice and admitted that he has conducted urine tests on patients who have been prescribed opioids. Ex. F (Candiotti Dep.) at 166:18-167:7; Ex. H (Consent form) ("I will submit to … urine...tests as requested by my physician to monitor my treatment.").

Alvogen's ANDA Product as directed by his or her physician, and Alvogen will induce that infringement.

3. Alvogen intends to induce infringement of '760 patent claims 1-4 and 11

Alvogen will induce patients (either alone or jointly with physicians) to directly infringe '760 patent claims 1-4 and 11 because Alvogen's Label encourages, recommends, and promotes that infringement. [redacted]

[redacted]

Alvogen asserts only that it is not liable for induced infringement because the instructions and data pertaining to hepatic impairment in Alvogen's Label were required or suggested by the FDA. *See, e.g.*, Ex. E (Candiotti Rebuttal Report) at ¶ 68. But the Federal Circuit rejected that argument in *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060-61 (Fed. Cir. 2010) (FDA requirements do not absolve an ANDA owner of specific intent to induce infringement); *see also Hoffman-La Roche*, 2010 U.S. Dist. LEXIS 92264, at *21 (same); *Eli Lilly*, 676 F. Supp. 2d at 378 (same). Alvogen's "decision to continue seeking FDA approval of those instructions" is "sufficient evidence of specific intent to induce infringement." *Eli Lilly*, 845 F.3d at 1368.

As demonstrated in the claim charts below, patients with mild or moderate hepatic impairment (either alone or with physicians) will directly infringe '760 patent claims 1-4 and 11 upon administration of Alvogen's ANDA Product in a dosage that has not been adjusted, and Alvogen intends this result:

'760 Patent, Claim 1	**Alvogen's ANDA Product**
"A method of treating pain"	[redacted]
"in a patient having mild or moderate hepatic impairment, the method comprising: administering to the patient having mild or moderate hepatic impairment"	

	[redacted]
"a starting dose of an oral dosage unit having hydrocodone bitartrate as the only active ingredient,"	
"wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate,"	
"and wherein the starting dose is not adjusted relative to a patient without hepatic impairment"	
'760 Patent, Claim 2	
"The method of claim 1, wherein"	
"the dosage unit provides a release profile of hydrocodone that does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 30%,"	
"and the release profile of hydrocodone does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an	

amount of more than 50%."	[redacted]
'760 Patent, Claim 3	
"The method of claim 1, wherein"	
"the dosage unit provides a release profile of hydrocodone that does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%,"	
"and the release profile of hydrocodone does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 30%"	
'760 Patent, Claim 4	
"The method of claim 1, wherein"	
"the dosage unit provides a release profile of hydrocodone that does not increase average hydrocodone C_{max} in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 9%,"	
"and the release profile of hydrocodone does not increase average hydrocodone C_{max} in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%."	
'760 Patent, Claim 11	
Claim 9 (for which claim 11 depends): "The method of claim 1, wherein"	
"the dosage unit provides a release profile of hydrocodone such that: (1) the average hydrocodone $AUC_{0\text{-}inf}$ per 20 mg of hydrocodone bitartrate dosed to subjects not suffering from renal or hepatic impairment is in the range of about 300 ng*h/mL to about	

500 ng*h/mL;"	[redacted]
"(2) the average hydrocodone $AUC_{0\text{-}inf}$ per 20 mg of hydrocodone bitartrate dosed to subjects suffering from mild hepatic impairment is in the range of about 300 ng*h/mL to about 570 ng*h/mL; and"	
"(3) the average hydrocodone $AUC_{0\text{-}inf}$ per 20 mg of hydrocodone bitartrate dosed to subjects suffering from moderate hepatic impairment is in the range of about 300 ng*h/mL to about 700 ng*h/mL."	
Claim 11: "The method of claim 9, wherein the dosage unit provides a release profile of hydrocodone such that the average hydrocodone $AUC_{0\text{-}inf}$ per 20 mg of hydrocodone bitartrate dosed to subjects suffering from moderate hepatic impairment is in the range of about 352 ng*h/mL to about 666 ng*h/mL."	

As the claim charts above make clear, there is no genuine dispute that patients with mild or moderate hepatic impairment (either alone or with physicians) will directly infringe '760 patent claims 1-4 and 11, and Alvogen intends this result. Alvogen is liable for induced infringement of these claims.

V. CONCLUSION

For the foregoing reasons, Pernix respectfully requests that the Court enter judgment that Alvogen induces infringement of the asserted claims of the '760 and '499 patents.

Respectfully submitted,

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March 16, 2018

CERTIFICATE OF SERVICE

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